FINDING OF NO SIGNIFICANT IMPACT

for

MATRIX™ (Altrenogest) Solution 0.22% for Cycling Gilts

Intervet, Inc.
Millsboro, DE

For Public Display
(HFA-305)

NADA 141-222

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The Center for Veterinary Medicine has considered the potential environmental impact of this action and has concluded that this action will not have a significant impact on the quality of the human environment and therefore an environmental impact statement will not be prepared.

Intervet, Inc., has submitted a new animal drug application (NADA) for the approval of MATRIX™ (altrenogest) solution 0.22% to synchronize estrus in cycling gilts. The product is currently approved for use in mares to suppress estrus. In support of the application, the drug sponsor has submitted a Phase I Environmental Impact Assessment in accordance with VICH guidelines for the environmental assessment of veterinary medicinal products.

We have reviewed the submission and determined that the environmental impact assessment provides sufficient information to determine that the proposed use is not expected to result in significant environmental impacts. Based on the VICH guidelines phase I decision tree, and the lack of information indicating that extraordinary circumstances may exist, a phase II assessment for the use of altrenogest is not required. The estimated soil concentration of 1.70 ug/kg is well below the phase II trigger of 100 ug/kg soil. Estimated aquatic concentrations in a static farm pond (estimated from EPA Generic Estimated Environmental Concentration Model) are below 20 ng/L (ppt). Concentrations in streams and rivers would be further reduced. We conclude based on sorption characteristics, physicochemical properties and exposure scenarios, that environmental exposures are expected to be very low and partitioning in soils and sediments would limit the amount of bioavailable altrenogest to terrestrial organisms and the amount entering aquatic systems. In addition, significant levels of altrenogest residues would not be expected to enter aquatic systems on a continuous basis. Therefore, chronic exposures would not be expected and potential impacts on aquatic reproduction parameters would be unlikely.

We have reviewed the EA and find that it is adequate to determine that significant environmental impacts are not expected from the approval of the NADA for the product.

09-30-03
Date

Steven D. Vaughn DVM
Director, Office of New Animal Drug Evaluation, HFV-100

Attachment: Environmental Impact Assessment

REGU-MATE FOR SWINE

ENVIRONMENTAL IMPACT ASSESSMENT

1. INTRODUCTION

Regu-Mate is an oral progestin product for use in swine. The active ingredient is altrenogest, a synthetic progestin. Regu-Mate is currently approved for use in mares to suppress estrus, thereby allowing for a predictable occurrence of estrus following drug withdrawal. The product will also be used to synchronise estrus in cycling gilts, and is administered by top dressing the animals' feed.

This document summarises the information relevant to the assessment of the environmental impact of Regu-Mate when used as instructed in swine.

2. COMPOSITION OF REGU-MATE

Regu-Mate is formulated as an oil-based solution for oral administration and has the following composition:

	$mg.ml^{-1}$
Altrenogest	2.20
Butylated hydroxyanisole	0.07
Butylated hydroxytoluene	0.07
Hydrogenated vegetable oil (Neobee®)	928.16

The product is supplied in 1 litre plastic bottles with a screw cap.

3. USE PATTERN OF REGU-MATE

In swine, Regu-Mate will be used to synchronise estrus in cycling gilts. The product is administered orally at a rate of 6.8 ml (15 mg altrenogest) per head, once daily for 14 consecutive days. One half of the daily feed allowance is top-dressed with Regu-Mate, and when this portion has been consumed, the remainder of the day's feed is provided.

In the US, sow farms typically range in size from about 150 to 3400 sows, with most modern farms having more than 1000 sows. The annual replacement rate for sows is typically about 45%, and therefore, the number of gilts entering production over one year would be about 68 to 1530. On most farms, 2-3 gilts are purchased for every one gilt that enters production and the total number of gilts on a farm in one year would range from about 170 to 3825 (assuming an average of 2.5 gilts purchased for one gilt entering production). Most farms receive shipments on a monthly basis, and therefore, the number of gilts receiving Regu-Mate at a single point in time would be about 15 to 320, assuming that all the animals were treated.

4. PHYSICO-CHEMICAL PROPERTIES

Altrenogest is a synthetic progestin with the following characteristics:

Name: Altrenogest

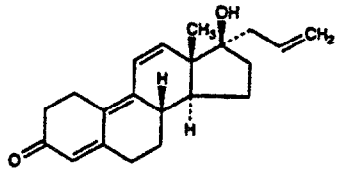
Chemical name: 17α-allyl-17-hydroxyestra-4,9,11-trien-3-one

CAS number: 850-52-2

Molecular formula: $C_{21}H_{26}O_2$

Molecular weight: 310.44

Structural formula:



Synonyms: Allyl-trenbolone, RU-2267, A-35957

The assay specification limit for altrenogest used in Regu-Mate is 98.0-102.0%. The specification limits for impurities are no more than 0.5% of individual related substances and no more than 2% total related substances.

Altrenogest has the following physico-chemical properties:

Melting point: 120°C (1)

Water solubility: 16.5 $mg.l^{-1}$ at 25°C (2)

Partition coefficient: K_{ow} (n-octanol/water) = 6100 (3)

Vapour pressure : 1.25×10^{-11} Torr at 25°C (4)

Soil adsorption/desorption:

Determined with 3 types of soil over the concentration range 21.3 to 213 $\mu g.l^{-1}$ (5):

Soil Type	Adsorption (%)	Desorption (%)	K_{oc}
Sandy loam	82.2-94.8	2.7-9.4	751-2950
Loamy sand	86.4-92.7	10.6-16.5	764-1510
Sandy silt loam	88.4-94.8	2.4-7.8	1230-2920

Biodegradation in soil:

Determined with 3 types of soil (sandy loam, clay loam, sandy silt loam) at an altrenogest concentration of 246 $mg.kg^{-1}$ (6). The test duration was 64 days.

Altrenogest was not readily biodegradable in any of the 3 soil types at the high test concentration used. In 2 of the soils, carbon dioxide production was slightly reduced relative to untreated soil.

5. ENVIRONMENTAL EXPOSURE

A Phase I environmental impact assessment for Regu-Mate has been conducted in accordance with the relevant VICH guideline (7). Under this guideline, a Phase I Decision Tree is followed to ascertain whether a Phase II assessment is necessary for the product under consideration (see Figure 1).

5.1 Questions 1-7 of the Phase I Decision Tree

For Regu-Mate, the answer to Questions 1 to 4 is No. Although the use of Regu-Mate in swine is restricted to treatment of gilts for synchronisation of estrus, the answer to Question 5 is also considered as No, based on the use pattern described in Section 3 above.

Regarding Question 6, the metabolism of altrenogest in swine has been investigated after single and multiple oral doses of radiolabelled altrenogest (8). The pattern of radioactive components in urine and bile was examined by thin layer chromatography, before and after treatment of the samples with deconjugating enzyme. The pattern of components was very similar after both single and multiple doses.

In untreated urine, about three-quarters of the radioactivity was associated with one very polar component and only relatively small amounts of free steroids, including parent compound, were detected. After deconjugation treatment, one major and 3 minor components were liberated, and the major component (*ca* 25% of the radioactivity) was confirmed as altrenogest by mass spectroscopy.

In untreated bile, the bulk of the radioactivity was in the form of polar material (93 and 59% of the radioactivity after single and multiple dosing respectively). After deconjugation treatment, there was a moderate increase in the proportion of other less polar components, none of which appeared to correspond to altrenogest.

In conclusion, the data indicate that altrenogest does not meet the definition of 'extensively metabolised' given under Question 6 in the VICH guideline ('no single fraction in excreta exceeds 5% of the total excreted radioactivity').

Regu-Mate is used to treat terrestrial species, and therefore, Questions 14 to 17 of the Decision Tree are relevant for estimating the environmental exposure to the product.

5.2 Questions 14-17 of the Phase I Decision Tree

The gilts treated with Regu-Mate will be housed throughout treatment and excreta collected from the treated animals could be spread onto agricultural land as fertiliser. The predicted environmental concentration (PEC) of the product in soil can be calculated using the model of Spaepen *et al* cited in the VICH guideline (9). This calculation is conservative as it uses a total residue concept combining parent drug and all related metabolites excreted by the animal in the calculation of the PEC. No allowance is made for the possible metabolism of altrenogest in swine to inactive or less biologically active metabolites. In addition, it is assumed that there is no degradation of altrenogest in swine excreta during its storage before spreading as fertiliser.

5.3 Predicted Environmental Concentration in Soil (Question 17)

The calculation of the PEC_{soil} involves the following steps:

1. Estimating the concentration of the drug in excreta.
2. Calculating the concentration of the drug in the soil.

The calculation is based on the assumption that the excreta are spread as manure on the land once a year.

Concentration of Drug in Excreta

For the purposes of the calculation, a farm of 2000 sows is used. Assuming an annual replacement rate for sows of 45% and the purchase and treatment of 2.5 gilts for each sow replaced, the total number of gilts treated in one year on a 2000 sow farm is:

$$2000 \times \frac{45}{100} \times 2.5 = 2250 \text{ gilts}$$

Therefore, the total annual dose of Regu-Mate administered is:

$15 \text{ mg.day}^{-1} \times 14 \text{ days} \times 2250 = 472{,}500 \text{ mg}$

Shipments of gilts are normally received monthly. Therefore, on a 2000 sow farm with a 45% annual replacement rate, 75 sows (900/12) are replaced each month by approximately 188 gilts (900 x 2.5/12). Thus, in Month 1 the total number of sows and gilts is approximately 2113, and in Month 12 the total number is approximately 3350. The 'average' number of sows and gilts over one year is:

(2113 + 3350)/2 = 2732 animals

Assuming a daily excreta production of *ca* 7 kg (1.5 gallons) per gilt, and assuming that sows produce the same amount of excreta as gilts (and ignoring excreta output by the litters), the total excreta produced per year is:

7 $kg.day^{-1}$ x 365 days x 2732 sows/gilts = 6,980,260 kg per year

Therefore, the concentration of drug in excreta from the treated gilts is:

472,500 mg/6,980,260 kg = 0.068 $mg.kg^{-1}$ (68 $\mu g.kg^{-1}$)

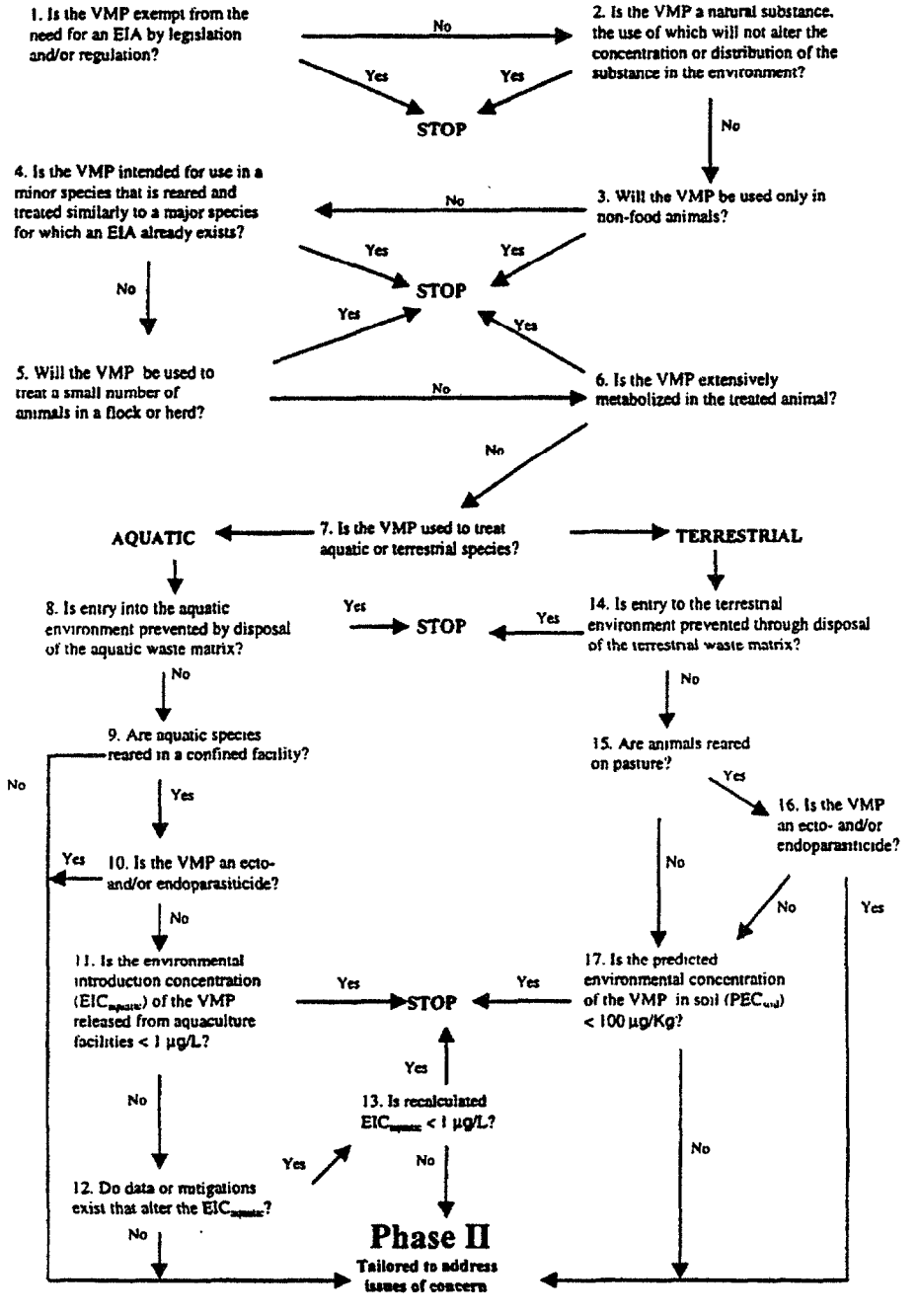
Predicted Concentration of Drug in the Soil

The estimation of PEC_{soil} requires an assumption of the annual quantity of excreta which will be spread as manure. The model of Spaepen *et al* derives this figure from the maximum amounts of nitrogen and phosphorus which can be applied as fertiliser in European countries. This approach is not directly applicable to the US situation, and therefore, the amount of manure applied to soil is taken from an AHI guideline (10). For swine, the figure is 22.7 x 10^3 kg manure per acre. It is assumed that the manure is ploughed into the soil, and that the average depth of the furrow is 15 cm. This corresponds to a weight of soil in one acre of 910,500 kg, assuming an average bulk density for soil of 1500 $kg.m^{-3}$.

Therefore, applying 22.7 x 10^3 kg manure containing a drug concentration of 68 $\mu g.kg^{-1}$ results in a concentration of the drug in soil of:

$$\frac{68\ \mu g.kg^{-1} \times 22.7 \times 10^3\ kg}{910.5 \times 10^3\ kg} = 1.70\ \mu g.kg^{-1}$$

Figure 1. Phase I Decision Tree



6. ENVIRONMENTAL EFFECTS

The estimated environmental concentration of altrenogest of 1.70 $\mu g.kg^{-1}$ is one-sixtieth of the PEC_{soil} threshold of 100 $\mu g.kg^{-1}$ required to trigger a Phase II assessment, involving environmental effects testing. Nevertheless, the potential effects of altrenogest on soil organisms have been investigated in 2 studies:

6.1 Effects on Soil Carbon and Nitrogen Cycle Micro-organisms

Altrenogest was incorporated in 2 soil types, a light sandy loam and a clay loam, at concentrations of 0.37 and 3.7 $mg.kg^{-1}$ (11). Each soil was supplemented with lucerne meal as a source of nitrogen, and excreta slurry (faeces and urine) from untreated pigs was also incorporated into the soils (38 g slurry per kg soil). The amount of carbon dioxide evolved and the soil content of ammonium, nitrate and nitrite were determined over a period of 70 days.

In the sandy soil, there was a small statistically significant decrease in CO_2 production from Day 42 onwards at the higher altrenogest concentration. In the clay soil, there was a small statistically significant increase in CO_2 production from Day 21 and Day 42 in the soil containing 3.7 and 0.37 mg altrenogest.kg^{-1} respectively.

Altrenogest at both concentrations had no consistent or statistically significant effects on nitrate production in either test soil.

6.2 Effects on Growth of Higher Plants

The effect of altrenogest on seed germination and subsequent growth of lettuce, radish, soya and wheat was investigated at concentrations in soil of 0, 1, 10 and 100 $mg.kg^{-1}$ (12). Phytotoxicity, crop emergence and crop vigour were assessed at regular intervals for up to 7 weeks and the plants were then harvested and the fresh and dry weight of roots and shoots determined.

All 4 crops germinated successfully and no phytotoxic response or abnormal growth effect was observed at any time in the altrenogest treated groups.

No significant effects were seen on crop emergence or vigour in lettuce and radish, or on crop emergence in wheat. There was a significant dose-related decrease in soya crop emergence (25% decrease at 100 $mg.kg^{-1}$) and a transient decrease in soya and wheat crop vigour at 100 $mg.kg^{-1}$.

There was no significant overall effect on fresh and dry weight of radish and wheat plants. A dose-related decrease in lettuce fresh weight was observed (20% decrease at 100 $mg.kg^{-1}$), but dry weight was not significantly altered by altrenogest treatment. Soya plant fresh weight and dry weight showed a dose-related reduction (30-35% decrease at 100 $mg.kg^{-1}$).

7. CONCLUSIONS

The use of Regu-Mate in swine is restricted to the treatment of gilts to synchronise estrus. A Phase I environmental impact assessment in accordance with the proposed VICH guideline indicates that environmental exposure to the product will be low. The PEC_{soil} for total altrenogest-related material arising from the spreading of excreta from treated gilts on agricultural land is well below 100 $\mu g.kg^{-1}$. Therefore, a Phase II assessment is not necessary for Regu-Mate. Furthermore, altrenogest had no significant effects on soil micro-organisms and plants when tested at concentrations which were at least 200-fold greater than the PEC_{soil}.

It can be concluded that use of Regu-Mate in swine in accordance with the product's recommended use instructions will have no significant impact on the environment, and no further studies are required in this area.

8. REFERENCES

1. Merck Index, 12th Edition, 1996.

2. Altrenogest (RU 2267). Determination of water solubility.
Roussel Uclaf, STE-026-A-20-1, July 1985.

3. Altrenogest (RU 2267). Determination of n-octanol/water partition coefficient.
Roussel Uclaf, STE-026-A-19-1, May 1985.

4. Altrenogest (RU 2267). Determination of vapour pressure.
Roussel Uclaf, STE-026-A-18-1, March 1985.

5. The assessment of adsorption/desorption of altrenogest in soils.
Huntingdon Research Centre, RSL 770/881035, 4 January 1989.

6. Biodegradation in soils of allyl-trenbolone.
Huntingdon Research Centre, RSL 727/861531, 27 February 1987.

7. Environmental impact assessment (EIAs) for veterinary medicinal products (VMPs) – Phase I.
VICH GL6 (Step 4), October 1998.

8. Tissue distribution of radioactivity and patterns of metabolites following single and multiple oral doses of ^{3}H-altrenogest to pigs.
Huntingdon Research Centre, RSL 616/84177, 13 June 1985.

9. Spaepen K R I *et al* (1997)
A uniform procedure to estimate the predicted environmental concentration of the residues of veterinary medicines in soil.
Environmental Toxicology and Chemistry, 16: 1977-82.

10. Guidance for industry for environmental risk assessment covering new animal drug applications for veterinary use.
Animal Health Institute, 21 August 1996.

11. The effects of altrenogest on soil carbon and nitrogen cycle micro-organisms.
Huntingdon Research Centre, RSL 754/88116, 18 January 1989.

12. Glasshouse evaluation of the effects of altrenogest on higher plant growth.
Agrisearch UK Limited, AS/1133/HR, 30 November 1989.

Signature block of responsible individual:

The undersigned official of Intervet Inc. certifies that the information presented in this environmental assessment is true, accurate and complete to the best of his knowledge.

S. Lee Whaley

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Intervet Inc.

28 January 2002
Date